

**EUROPEAN COMMISSION**

DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Directorate B - Health systems, medical products and innovation

B4 – Medical products: quality, safety, innovation

SUMMARY OF THE 2016 ANNUAL REPORTING OF SERIOUS ADVERSE REACTIONS AND EVENTS FOR TISSUES AND CELLS**(DATA COLLECTED FROM 01/01/2015 TO 31/12/2015)****EXECUTIVE SUMMARY**

Human tissues and cells for human application and assisted reproduction programmes provide important benefits for thousands of EU citizens every year. However, the use of any substance of human origin carries some risks, notably the possible transmission of a disease from the donor. These risks can be controlled and minimised by the application of safety and quality measures as laid down in EU legislation. Vigilance and surveillance programmes are one of the cornerstones of the system, allowing the identification and detection of risks and the application of corrective and preventive measures. In accordance with the legislation¹, EU Member States must submit to the European Commission an annual report on the notification of serious adverse reactions (SAR) and serious adverse events (SAE) received by the competent authority. The Commission, in turn, must send to the competent authorities of the Member States a summary of the reports received. Definitions for SAR and SAE are provided in the EU legislation².

Since 2008, the reporting countries (EU Member States and Liechtenstein and Norway) have submitted to the European Commission (henceforth referred to as 'the Commission') annual vigilance reports on the notification of SAR occurring in recipients of tissues and cells, and SAE which occur from donation to clinical application.

The Commission has been working with the Tissues and Cells Competent Authorities for several years to standardise data collection procedures and to improve both accuracy and comparability of the information submitted. The consistency and completeness of the data collection and submission to the Commission has improved over time. Discussions of the results between experts demonstrate that the SAR/SAE (henceforth referred to as 'SARE') reporting exercise works well, and assists countries across Europe in pinpointing and improving safety and quality in this field.

This report summarises the data collected by the reporting countries for the year 2015 and assesses them in the light of the information submitted in previous years. Some key findings of the reporting exercise are the following:

- The overall number of tissues and cells distributed in 2015 amounted to 2,102,332 units (322,389 non-reproductive, reported by 24 countries and 1,779,943 reproductive tissues and cells, reported by 20 countries). Twenty countries reported the number of recipients which

¹ Article 7 and Annexes III, IV and V of Directive 2006/86/EC

² Article 3 of Directive 2004/23/EC

amounted to 365,060 and 21 countries submitted data on the total number of tissues and cells processed which reached 2,280,512.

- A total of 246 SAR in recipients were reported by 16 countries, of which 74 were related to non-reproductive and 172 to reproductive tissues and cells. Data show that 18% of the SAR associated with the transplantation of non-reproductive tissues and cells were infections, mostly of bacterial or fungal origin. Most of the reported SAR for reproductive cells were related to the transmission of genetic diseases.
- A total of 622 SAE were reported by 21 countries (446 related to non-reproductive and 176 to reproductive tissues and cells), most of which occurred during procurement or processing and were mainly attributed to human error.
- Recognising the importance of donor adverse reactions, the Commission continues to collect such data on a voluntary basis. It is notable that the 2016 exercise showed a significant increase in the voluntary reporting of SAR in donors, with 615 cases reported by 17 countries, of which 2 cases resulted in the death of the donors. This data further emphasises the need for Tissues and Cells Competent Authorities to put in place appropriate follow-up and protection mechanisms for living donors of tissues and cells.

Before publication, the data contained in this report was presented at the Tissues and Cells Competent Authorities meeting in February 2017, allowing the reporting countries to verify their national data and to share experience and knowledge.

1. DATA COLLECTION METHODOLOGY

This report provides a summary of the data reported to the Commission in 2016 by all Member States, together with Liechtenstein and Norway, pertaining to the reporting period from 1st January to 31st of December 2015. It also includes comparisons with the data from previous years and draws general conclusions. The Commission provided the following tools to the participating authorities to promote a standardised approach to data reporting:

- 1) An electronic reporting template (template version 2.5) to be sent to a DG SANTE hosted database.
- 2) The Common Approach document for definition of reportable serious adverse events and reactions (henceforth referred to as the “Common Approach”) (version 2.5) providing guidance to the reporting countries when filling out the electronic reporting template³.

In December of 2016 a service contract agreement was signed between the Commission and the European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe, to carry out the verification and analysis of the 2016 SARE exercise and to draft the summary report. Early in 2017, the EDQM began contacting reporting countries in order to clarify and verify the accuracy of the reported data and performed the analysis of the information presented in this report.

2. MAIN FINDINGS OF THE 2015 DATA COLLECTION

2.1. Activity data (denominators)

As part of the reporting exercise, Member States are requested to provide data not only on SAR and SAE but also concerning their national activity. Although not legally binding, providing data on the

³ Over the years, the Common Approach document has been regularly updated. This has in turn, resulted in a gradual increase in the quality of the data collected from the Member States.

number of tissues distributed, the number of recipients and the number of tissues processed at national level facilitates a better overview and understanding of the different activities in the Member States and helps to put the data on SARE into context. In particular, the numbers of tissues and cells distributed and of recipients are used as denominators in the analysis of SAR and the number of tissues and cells processed is used as a denominator in the analysis of SAE.

As in previous years, many countries acknowledged that accurate activity data for certain types of tissues and cells were difficult to collect and some of them provided incomplete numbers for SAR denominators. A few countries could not provide data as the measurement units collected at national level are not harmonised among countries and do not always correspond to those requested during the EU exercise (e.g. assisted reproduction cycles vs. number of oocytes distributed, as requested in the current version of the reporting template). For non-reproductive tissues and cells, 24 countries reported data on units distributed (AT, BE, BG, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LV, MT, NL, NO, PT, SI, SE and UK) and 20 (AT, BG, CZ, DK, EE, ES, FI, FR, EL, HR, HU, IE, IT, LT, MT, NL, NO, PT, RO and SE) on recipients. For reproductive tissues and cells, 14 (AT, BE, DE, DK, EE, ES, HR, HU, IE, LV, MT, NL, SI and SE) and 10 countries (AT, BG, DK, ES, HR, IE, MT, NL, PT and SE) reported data on units distributed and number of recipients, respectively.

The overall number of *distributed* tissues and cells in 2015, as submitted by the reporting countries, amounted to 2,102,332 units (322,389 non-reproductive and 1,086,888 oocytes delivered for IVF, 455,248 sperm delivered for insemination or IVF and 235,781 embryos delivered for transfer. Additionally, 85 ovarian tissues and 1941 testicular tissue were distributed). This number had increased considerably compared to previous years – one of the reasons being that two countries reported reproductive numbers for the first time in the 2016 exercise.

The main types of non-reproductive tissues and cells distributed were skeletal tissues⁴ (192,037 units), followed by haematopoietic progenitor cells (HPC; 57,841 units) and ocular tissues (35,515 units). Refer to Figure 1 for further details.

⁴ The “general” category is used by Member States that do not collect data separately for each type of tissue or cell in some categories (i.e. musculoskeletal tissues vs. bone, cartilage, tendons/ligaments, and other musculoskeletal tissues such as meniscus or ear ossicles).

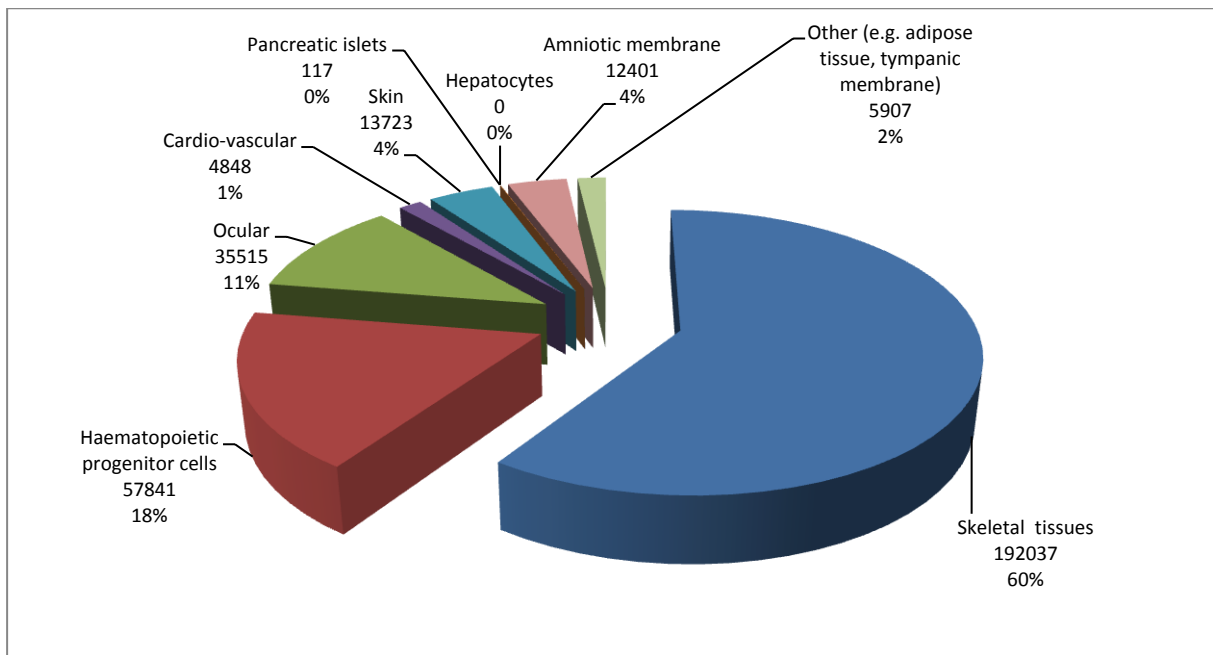


Figure 1. Total number of non-reproductive tissues and cells distributed (units); data 2015.

In 2015, 20 countries reported a total of 365,060 *recipients* (patients) having received tissues or cells. Of these, 109,312 were recipients of non-reproductive tissues or cells. Figure 2 shows the total number of patients that received each type of non-reproductive tissue or cell.

For reproductive cells, 255,748 patients underwent an assisted reproduction procedure involving partner or non-partner sperm, oocytes or embryos.

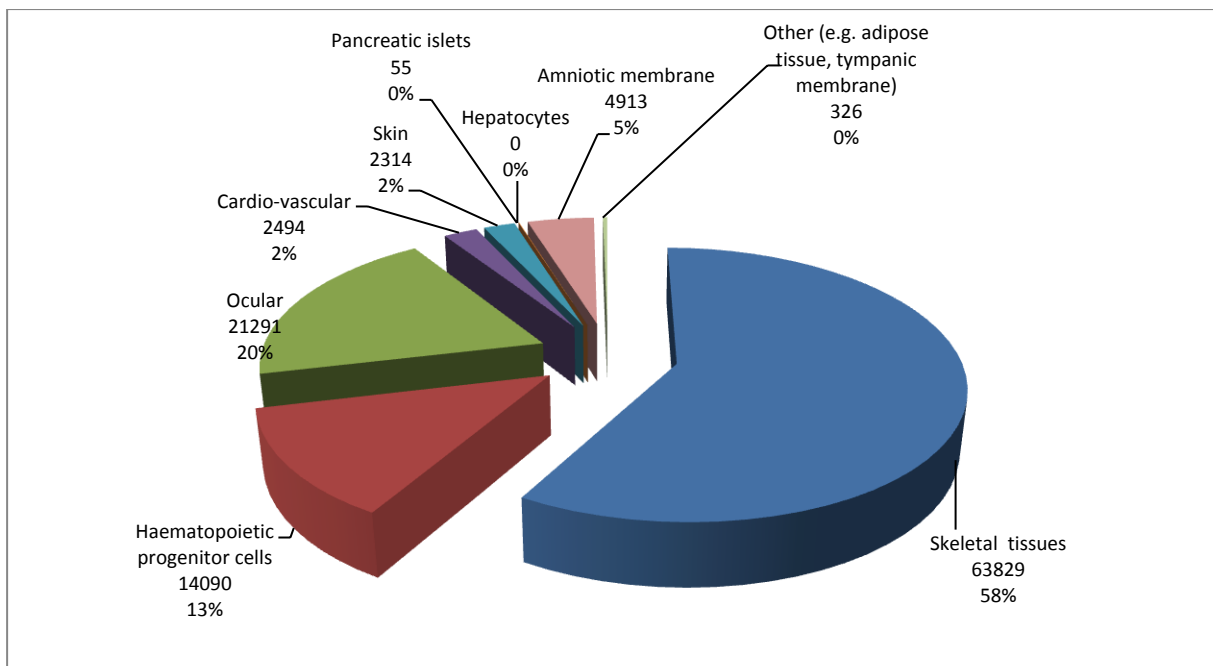


Figure 2. Total number of recipients per type of non-reproductive tissues and cells; data 2015.

An overview of the data for the SAR denominators for non-reproductive and reproductive tissues and cells provided by countries in the period between 2011 and 2016 (data pertaining to 2010-2015) are presented in Figure 3 and Figure 4, respectively.

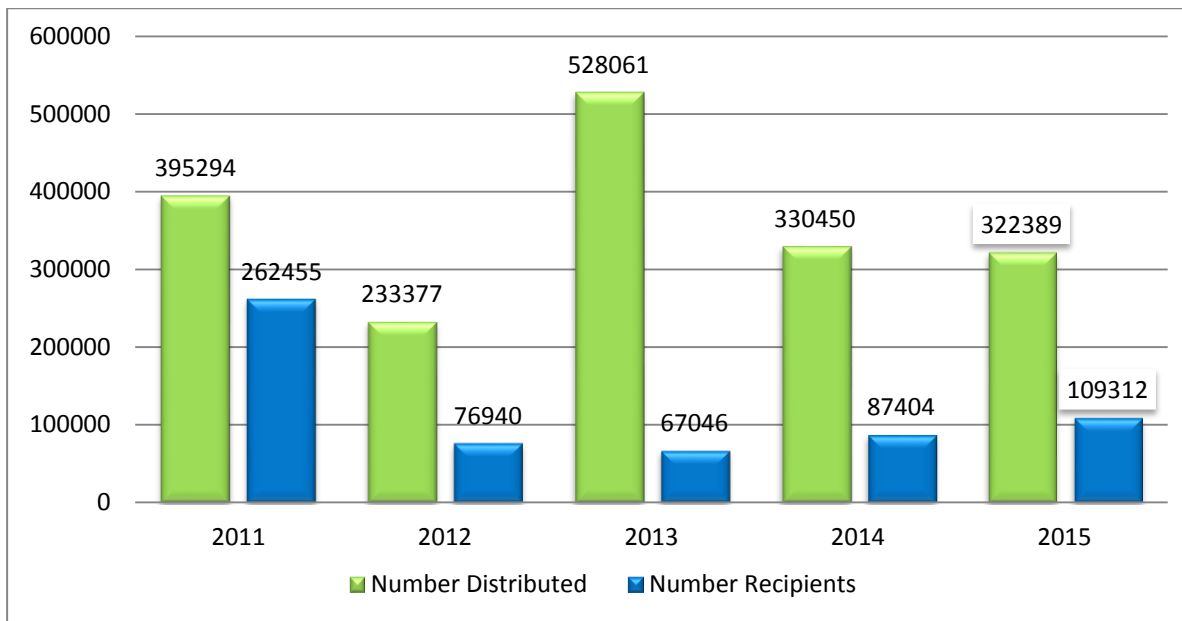


Figure 3. Total number of non-reproductive tissues and cells distributed (units) and number of recipients of human tissues and cells: 2010-2015 comparative data.

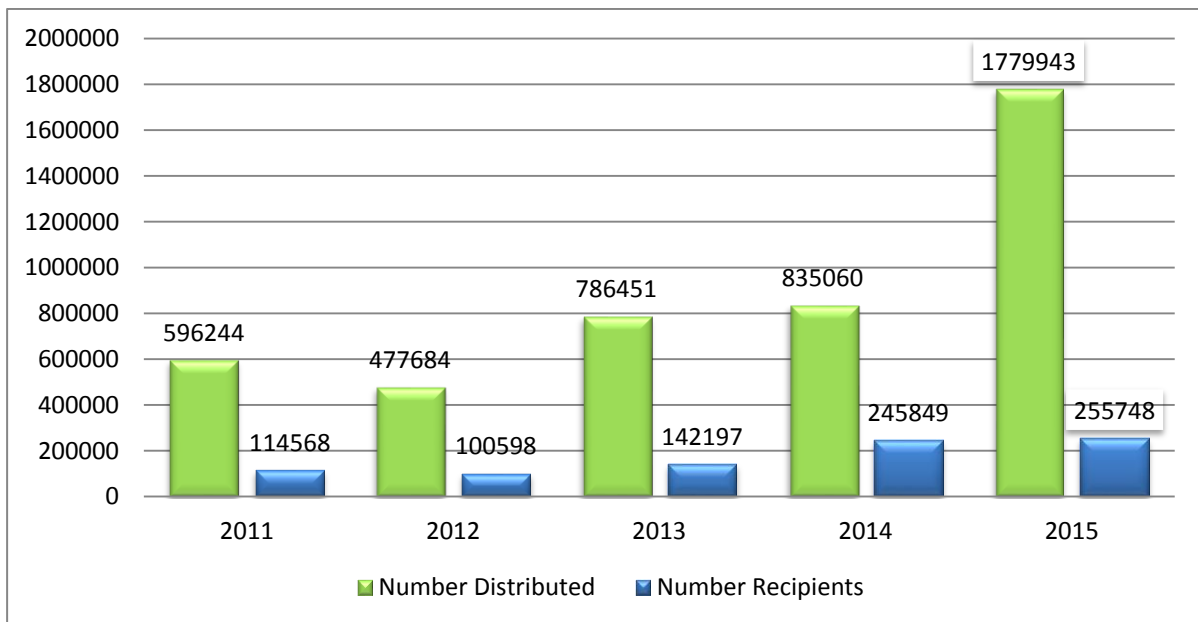


Figure 4. Total number of reproductive tissues and cells distributed (units) and number of recipients of human tissues and cells: 2010-2015 comparative data.⁵

Twenty one countries (AT, BG, CY, DE, DK, EE, EL, ES, HU, IE, IT, LT, LV, MT, NL, PL, PT, SK, SI, SE, UK) provided data regarding the number of tissues and cells *processed* in 2015. For the purpose of this reporting exercise, the term “tissues and cells processed” refers to tissues and cells processed in the tissue establishments, but not necessarily distributed to the end-users. Overall a total number of 2,280,512 tissues and cells were reported as processed in 2015.

The comparison data with previous exercises is presented in Figure 5.

⁵ As specified in the Common Approach document, this data includes the number of sperm units delivered to a clinic for insemination or to a laboratory for IVF, the number of oocytes delivered to a laboratory for IVF and the number of embryos delivered to a clinic for transfer to patients.

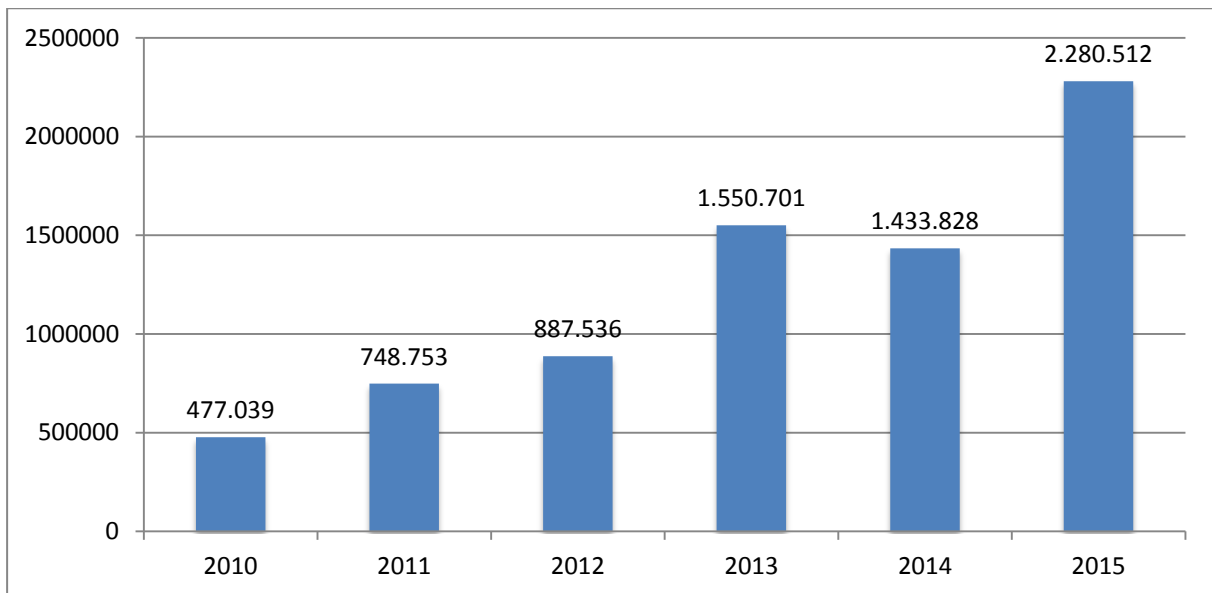


Figure 5. Total number of tissues and cells processed (units): 2010-2015 comparative data.

2.2. Serious Adverse Reactions

A total of 246 SAR were reported in 2015. Of these, 74 were related to non-reproductive and 172 to reproductive tissues and cells. Of the SAR reported for non-reproductive tissues and cells, at least 3 led to death⁶. The number of SAR reported by countries over the years for both categories (non-reproductive and reproductive tissues and cells) is presented in Figure 6.

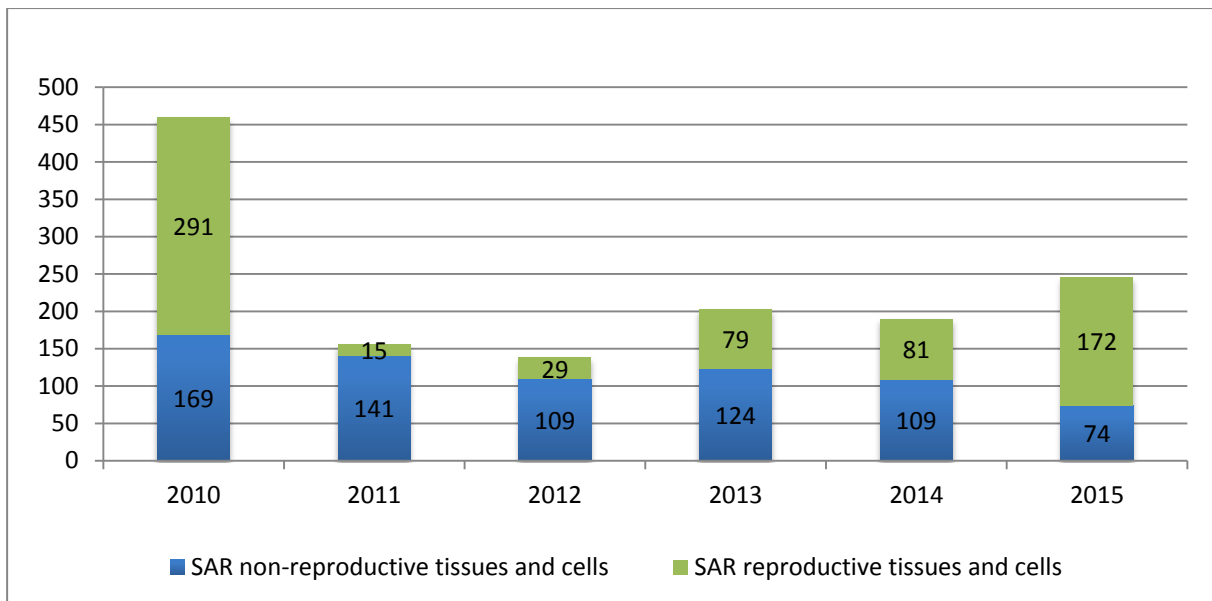


Figure 6. Total number of Serious Adverse Reactions: 2010-2015 comparative data⁷.

2.2.1 Information by country

⁶ Since reporting of deaths was not mandatory in the present exercise, it cannot be excluded that additional deaths occurred as a result of SAR but were not reported to the European Commission during this exercise.

⁷ 2010 SAR data also include 209 cases of ovarian hyperstimulation syndrome (OHSS) reported under SAR, which should have been reported as SAR in donors.

Fifteen Member States (CZ, DE, DK, EL, ES, FI, FR, IE, IT, LV, NL, PL, PT, SE, UK) and Norway reported SAR related to the clinical application of tissues or cells. On the other hand, 13 Member States (AT, BE, BG, CY, EE, HU, HR, LT, LV, MT, RO, SK, SI) and LI reported no recipient SAR in 2015. These data, as has been highlighted in previous reports, suggests that SAR reporting still needs to be improved at national level.

Twelve Member States (DE, DK, EL, ES, FR, IE, IT, NL, PL, PT, SE, UK) reported SAR related to the transplantation of non-reproductive tissues or cells, and 11 Member States (CZ, DE, DK, ES, FI, IE, IT, LV, PL, SE, UK) and Norway reported SAR following the clinical application of reproductive tissues or cells.

As mentioned above, the frequency of SAR can be put into context by calculating percentages in relation to the national activity data. Based on the data submitted, the percentage of SAR related to the use of non-reproductive tissues and cells among the reporting countries ranges from 0.013-0.439% SAR/# tissues and cells distributed and from 0.019-0.813% SAR/# of recipients. For reproductive cells, this range was 0.000-0.352% SAR/# tissues and cells distributed and 0.036-0.639% SAR/# of recipients.

However, these percentages should be interpreted with caution as they may not so much reflect the incidence of SAR and the improvement of quality and safety measures but rather the effectiveness and completeness of the national vigilance and reporting systems. Percentages calculated individually for each country having reported denominators have been made available to Member States, allowing them to benchmark their results against previous national exercises and with other Member States.

2.2.2 Data by type of tissue or cell

Out of the total 246 SAR reported:

- 74 (30%) were related to the transplantation of non-reproductive tissues or cells (see Figure 7). Of these:
 - 49 were related to the transplantation of haematopoietic progenitor cells (HPC) (17 bone marrow, 25 peripheral blood stem cells and 7 cord blood).
 - 25 were related to transplantation of replacement tissues (1 general³ musculoskeletal tissue, 7 bone, 2 tendons/ligament, 11 ocular tissue, 1 heart valve, 1 vessel, 1 skin and 1 adipose tissue).
- 172 (70%) were related to the clinical application of reproductive tissues and cells (64 sperm, 41 oocytes and 67 embryos) (see Figure 8).

No SAR were reported for cartilage, other musculoskeletal tissues, donor lymphocyte infusions (DLI), other HPC, other cardiovascular tissues, pancreatic islets, hepatocytes, amniotic membranes or ovarian and testicular tissues.

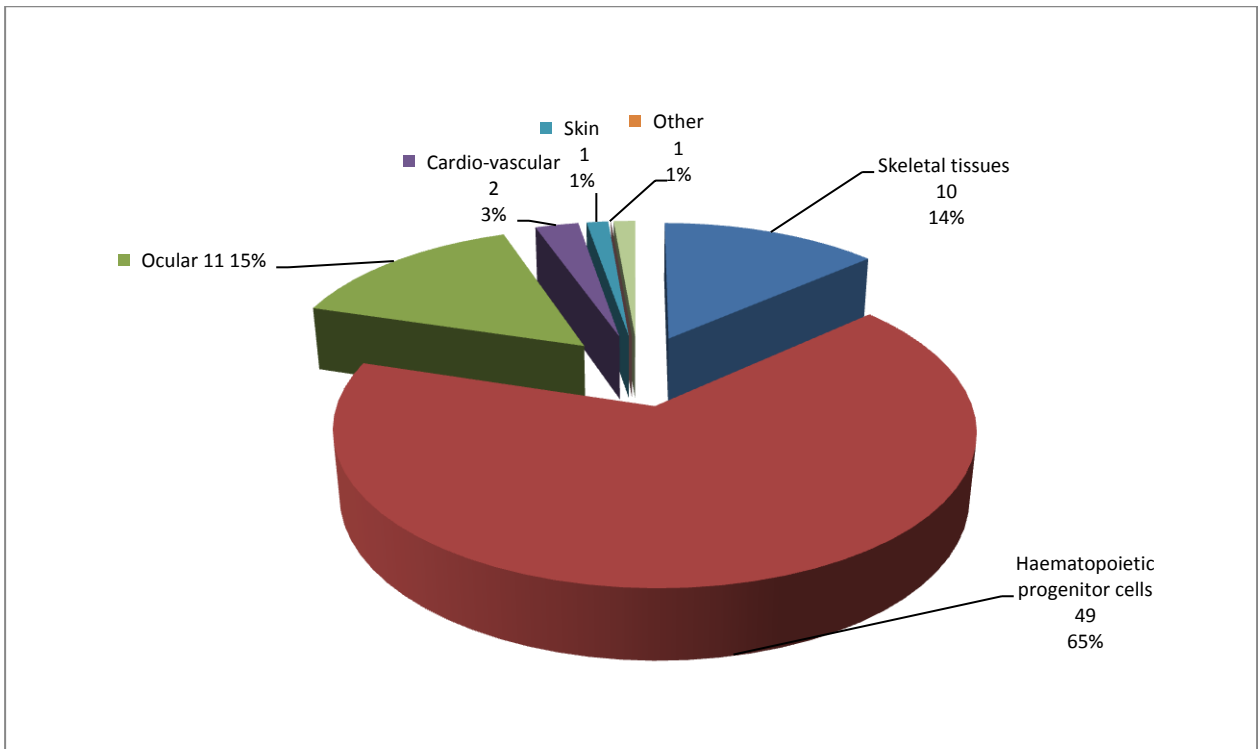


Figure 7. Number of SAR for each type of non-reproductive tissues and cells (absolute values and percentage of total recipient SAR); 2015 data.

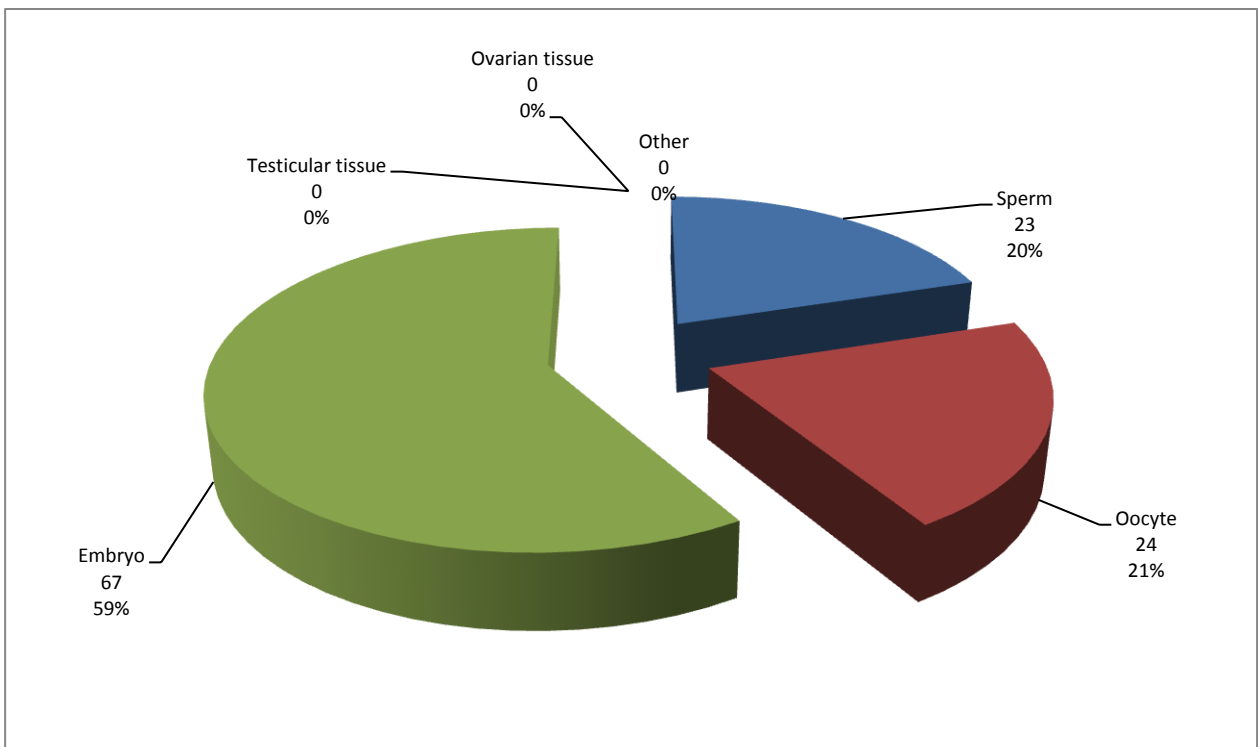


Figure 8. Number of SAR per each type of reproductive cells (absolute values and percentages of total recipient SAR); 2015 data.

2.2.3 Data by type of SAR

The 74 SAR related to the transplantation of **non-reproductive** tissues and cells were categorised as follows:

- Transmitted infections: 13 cases (17.6% of all reported SAR for non-reproductive tissues and cells; see Figures 9 and 10), divided as follows:
 - 8 cases of bacterial infections, reported for the following transplanted tissues/cells: 3 ocular tissues, 3 HPC, 1 musculoskeletal tissue and 1 adipose tissue.
 - 5 cases of other transmitted infections (all cases of fungal infections following transplantation of ocular tissues).

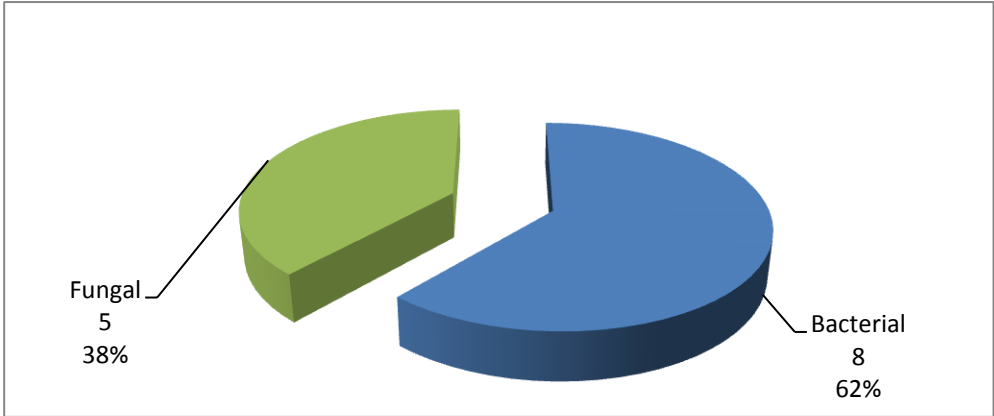


Figure 9. Transmitted infections in non-reproductive tissues and cells; data 2015.

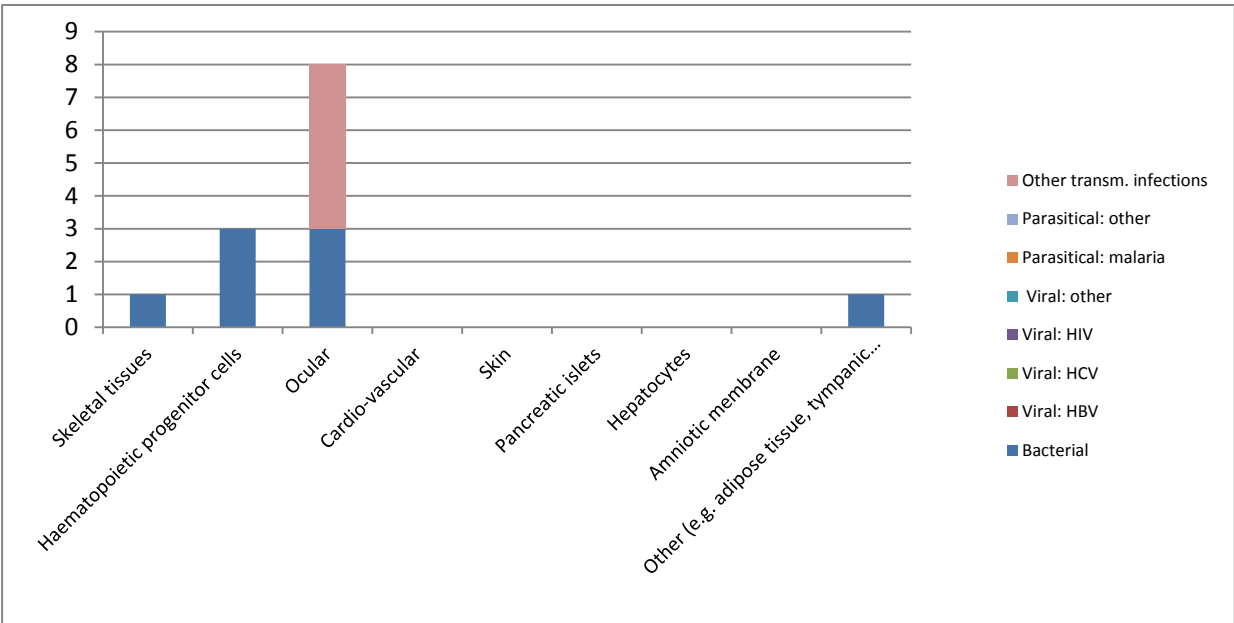


Figure 10. Transmitted infections per type of non-reproductive tissues and cells; data 2015.

- Other SAR: 61 cases (82.4% of all reported SAR for non-reproductive tissues and cells). In this broad and heterogeneous category:
 - 46 SAR concerned HPC transplantation (15 bone marrow, 24 peripheral blood cells and 7 cord blood).
 - 15 SAR related to the transplantation of other tissues (9 musculoskeletal, 3 ocular tissue, 1 heart valve, 1 vessel and 1 skin).

The 172 SAR associated with the application of **reproductive cells** were classified as follows (see Figure 11):

- Transmitted infections: 1 SAR (0.6% of all reported SAR for reproductive tissues and cells) related to the clinical application of an embryo (bacterial infection).
- Other disease transmissions (e.g. genetic diseases): 59 cases (34.3% of all reported SAR for reproductive tissues and cells) subsequent to assisted reproduction treatments using oocytes in 17 cases, sperm in 41 cases and embryo in 1 case.
- Other SAR: 112 cases (65.1% of all reported SAR for reproductive tissues and cells) related to the clinical application of embryos 65 cases, oocytes 24 cases and sperm 23 cases.

Of these 172 SAR, 101 were related to non-partner donation (62 sperm and 39 oocytes).

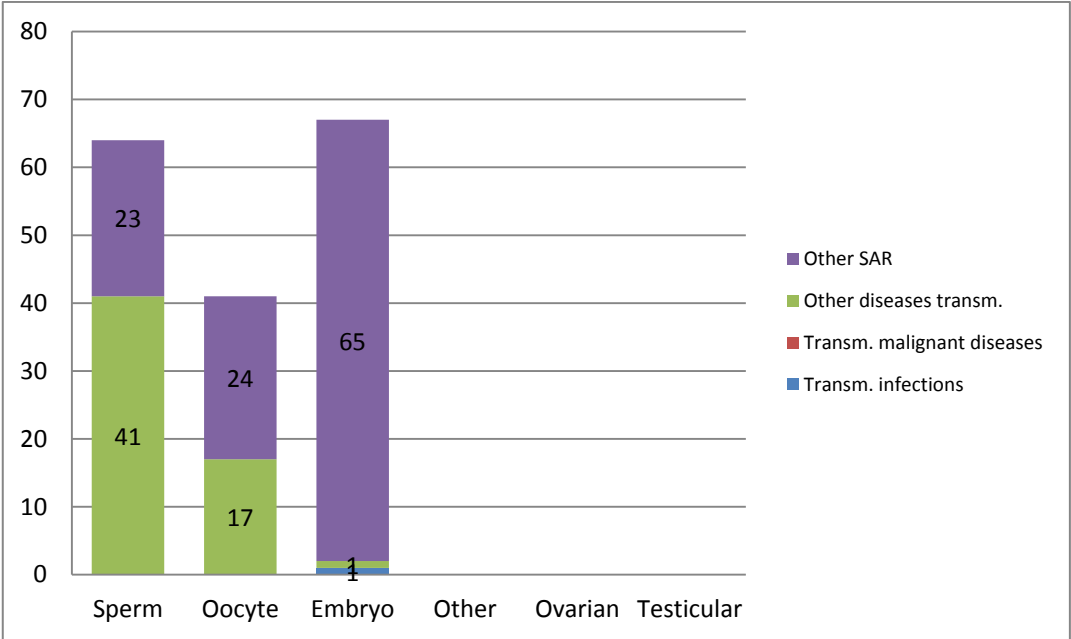


Figure 11. SAR related to the application of gametes and embryos; 2015 data.

2.3. Serious Adverse Events

The total number of SAE reported for 2015 was 622, showing that such events occurred for 0.027% of tissues and cells processed during this period. As mentioned previously in the case of SAR, the percentage of SAE in relation to the total number of tissues and cells processed should be interpreted with caution as not all countries reported these data. The total number reported in 2015 increased slightly when compared to previous years, as presented in Figure 12.

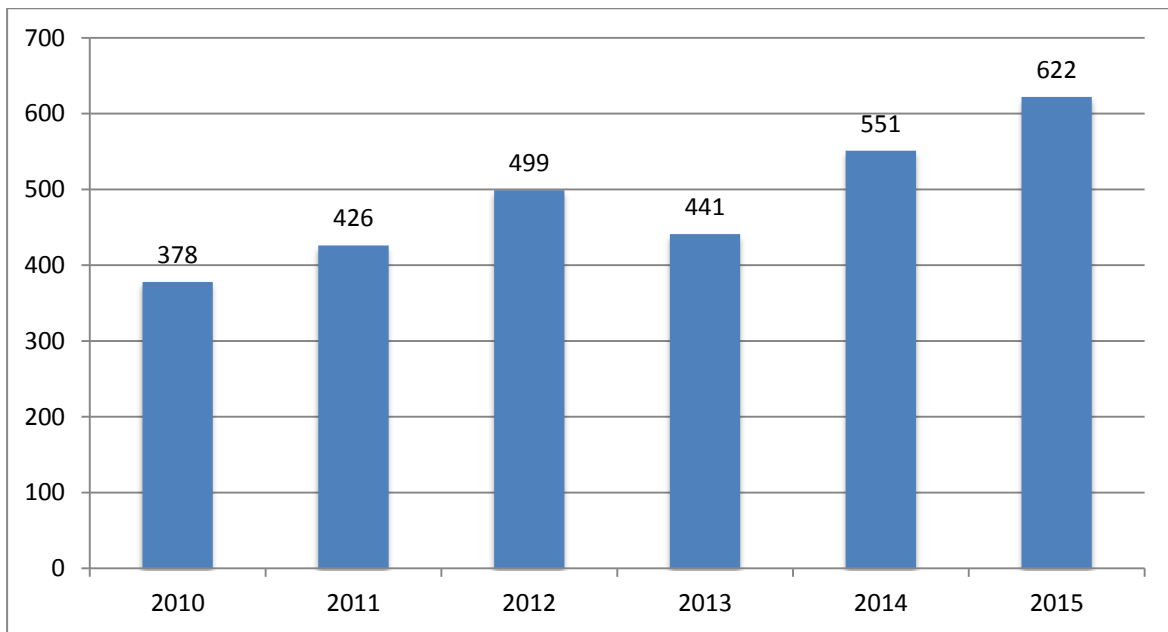


Figure 12. Total number of SAE reported: 2010-2015 comparative data.

The largest single cause of SAE was “human error” as was also the case in previous exercises. An overview of SAE types over the years is presented in Figure 13.

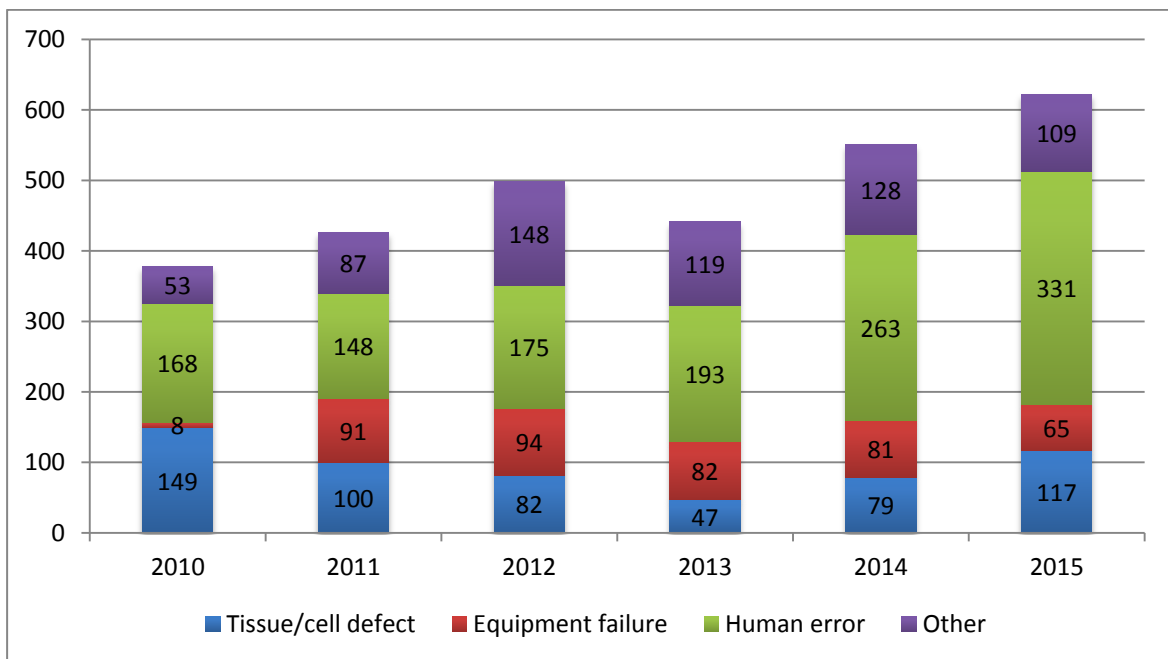


Figure 13. Total number of SAE reported categorised by origin: 2010-2015 comparative data.

2.3.1 Information by country

Eighteen countries reported SAE for non-reproductive tissues and cells (AT, BE, DE, DK, EE, ES, FI, FR, HU, IE, IT, NL, PL, PT, SI, SE, UK and NO) and 18 countries for reproductive cells (AT, BE, CZ, DK, ES, FI, FR, HU, IE, IT, LV, MT, NL, PT, SI, SE, UK and NO).

It is worth noting that, in some cases a single SAE affected a large number of tissues. In 2015 at least 1696 tissues or cells were affected by SAE.

2.3.2 Information by activity

The overview of the SAE reported by type of activity is presented in Figure 14.

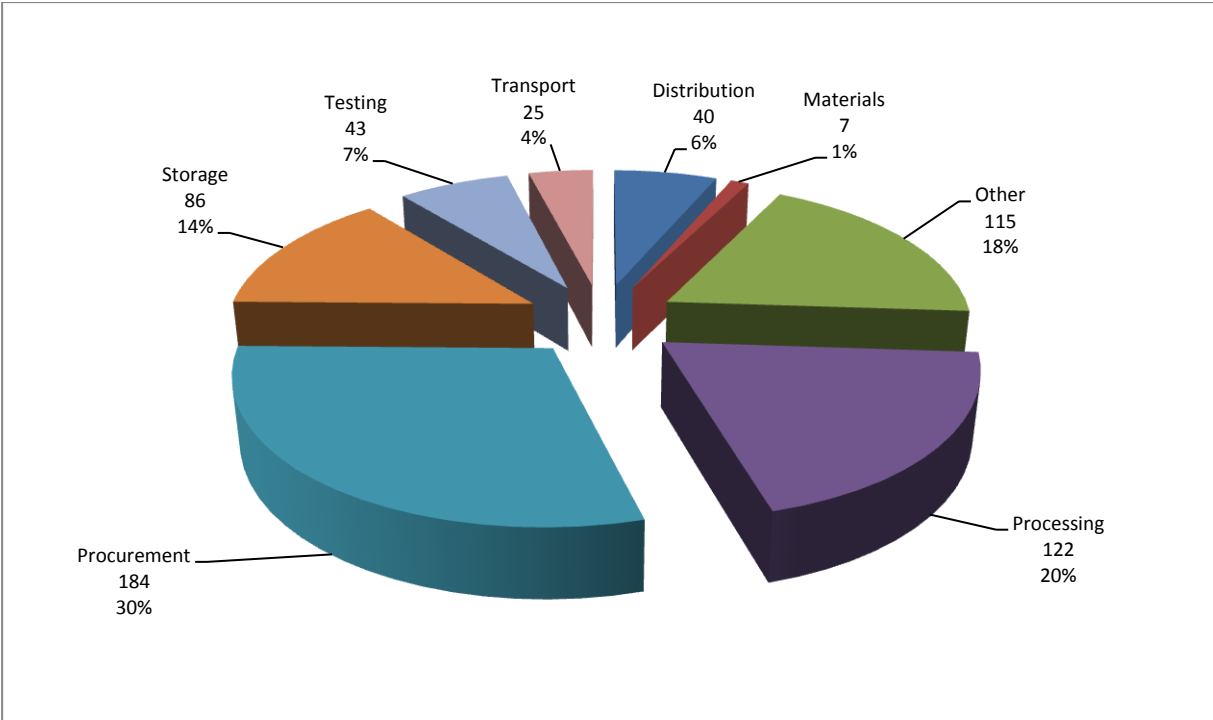


Figure 14. Number of SAE and percentage of total SAE reported by type of activity.

2.3.3 Information by type of SAE

The 622 SAE were classified as tissue or cell defects, human error, equipment failure and other types of events. The distribution per type is presented in Figure 15.

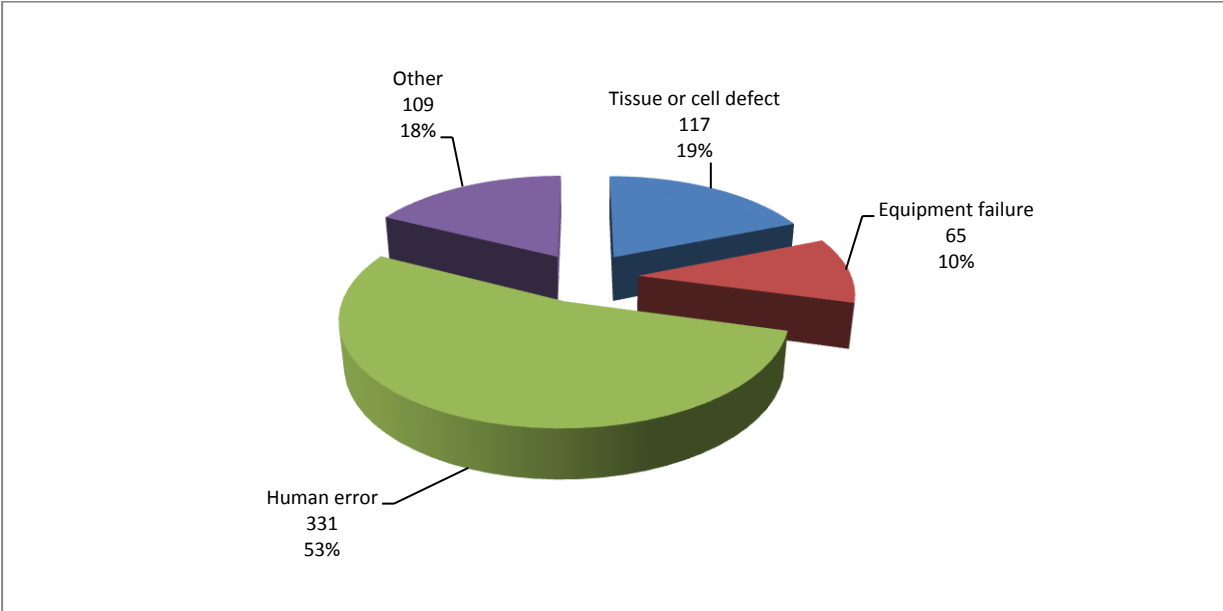


Figure 15. SAE types; 2015 data.

Taking into account the type of SAE and the stage at which they occurred during the donation-distribution chain, SAE were categorised as shown in Figure 16.

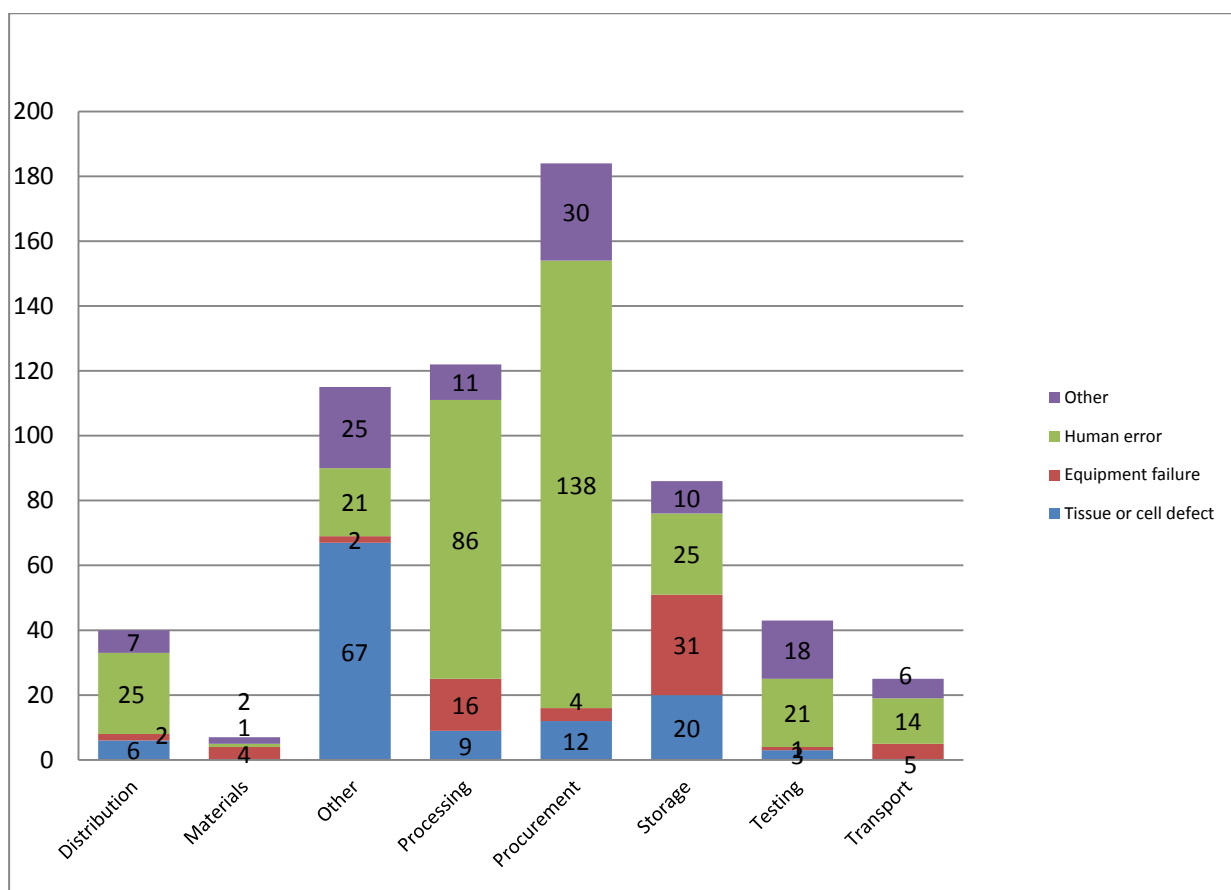


Figure 16. SAE per type and stage at which they occurred during the donation-distribution chain; data 2015.

SAE occurred mostly during the procurement and processing stages, with a significant number also reported under the “Other” category.

2.4 SAR in donors

As in previous exercises, SAR in donors were included in the annual report. Recognising the importance of all donor adverse reactions, including those not directly impacting the quality and safety of tissues and cells or those reported in pharmacovigilance systems (ovarian hyper-stimulation syndrome [OHSS] following oocyte donation, reactions subsequent to the administration of Granulocyte Colony-Stimulating Factor [GCSF] for collection of peripheral blood HPC, etc.) the Commission continues to collect such data on a voluntary basis in agreement with the Member State competent authorities.

In 2015, 17 Member States (AT, BE, BG, DE, EE, ES, HR, IE, IT, FI, FR, NL, PL, PT, SI, SE, UK) reported a total of 615 SAR in donors. Of those, 38 cases were related to the donation of non-reproductive tissues or cells (6% of all SAR in donors), reported by 8 Member States (BE, DE, ES, FI, FR, IT, NL, UK). All these 38 cases were associated with donation of HPC. These data are presented in Figure 17.

One SAR related to HPC donation resulted in the death of the donor. As vigilance systems are in place to protect donors and recipients, and donor deaths are particularly concerning given that donors are otherwise healthy individuals, the Commission and Member States have deemed it appropriate to include a specific field to report donor deaths in future SARE reporting exercises.

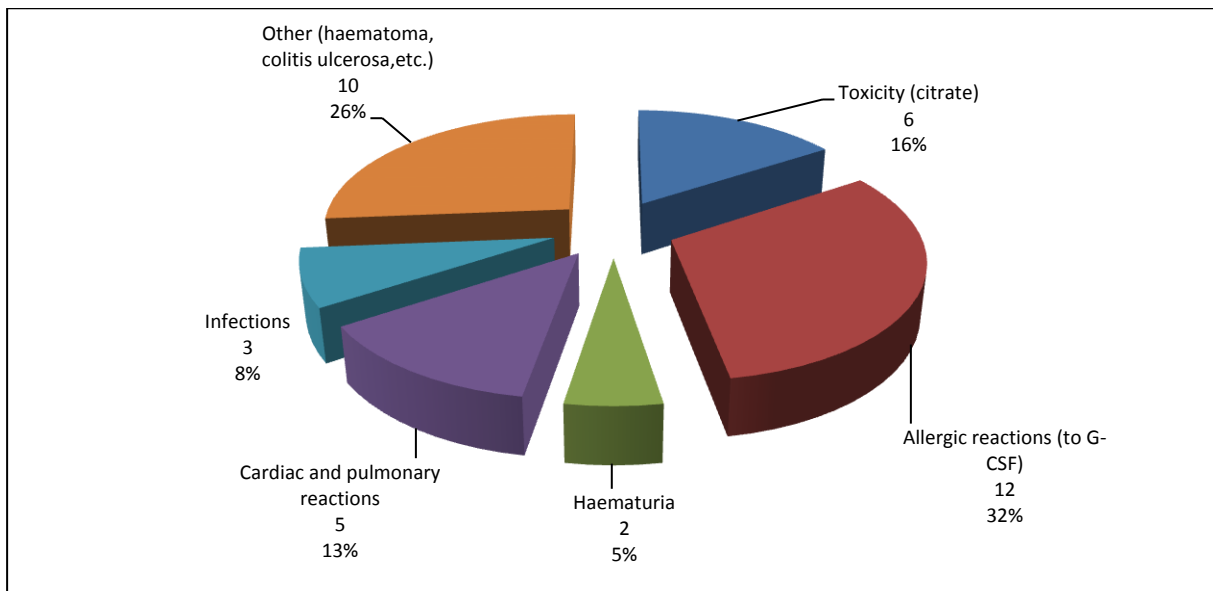


Figure 17. SAR in HPC donors, data 2015.

Of the total, 584 cases were related to SAR in oocyte donors (amounting to 94% of all SAR in donors) reported by 15 Member States (AT, BG, DE, EE, ES, FR, HR, IE, IT, NL, PL, PT, SI, SE, UK). One SAR related to oocyte partner-donation resulted in the death of the donor/patient.

SAR in donors of reproductive tissues or cells were reported under the following categories: oocytes general (49), oocytes for non-partner donation (22) and oocytes for partner donation (506).

In the case of non-partner donation the main SAR reported were severe OHSS (5), hemoperitoneum (13), pelvic inflammatory disease (2), bronchospasm secondary to anaesthesia (1) and adnexal torsion (1).

Most of the SAR in oocyte donors were critical, severe or moderate-to-severe OHSS cases (386 cases). Other types of SAR in donors reported included surgery and anaesthesia complications, infectious complications and other types of SAR (see Figure 18).

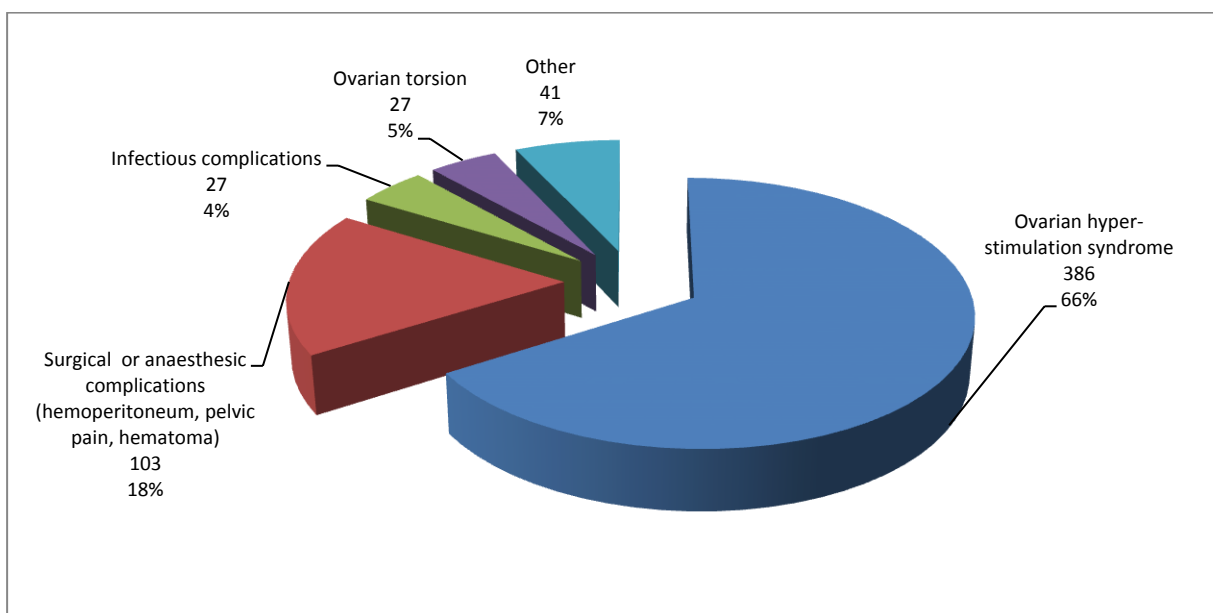


Figure 18. SAR in oocyte donors, 2015 data.

3. Conclusions

Overall, the implementation of vigilance requirements and data collection systems in the tissues and cells field appears to have improved over time.

The fact that most countries report data on the number of tissues and cells distributed but not all report the number of recipients suggests that more work is needed within the organisations responsible for human application. These are key actors for ensuring not only traceability of tissues and cells, but also effective vigilance systems. Health professionals involved in the clinical application of tissues and cells and tissue establishment personnel should be encouraged to submit reports in order to contribute to greater understanding and to identify preventive and corrective measures so that lessons learned can be shared with others to help avoid the repetition of SARE. It is worth noting that the lack of consensus on the most appropriate units for the collection of data for certain tissue and cell types (e.g. units of skin vs cm² vs m², or oocytes in units vs cycles) may explain why some countries choose not to, or were not able to, report data on SARE denominators.

In January 2017, a Vigilance Expert Sub-group (a sub-group to the Competent Authorities on Substances of Human Origin Expert Group, CASoHO E01718) was established by the Commission, in agreement with the Expert group, with agreed terms of reference that include supporting the development and improvement of the SARE reporting system. The future work of the sub-group should help to improve and harmonize the exercise and support the development of national SoHO vigilance systems. The work of the expert sub-group will also be important as the outcomes may contribute to the ongoing evaluation of the legal frameworks on blood, tissues and cells⁸.

The Joint Action VISTART⁹ which includes a work-package dedicated to vigilance reporting for blood, tissues and cells will conclude in 2018 and its outputs will be a further source of reflection for improving the implementation of vigilance requirements and SARE data collection.

As in previous exercises, the highest number of SAR related to the transplantation of non-reproductive tissues and cells were associated with infection – mostly of bacterial and fungal origin. In contrast, the most reported SAR for the clinical application of reproductive cells were genetic diseases. Thus, Commission and Member States have deemed it appropriate to include a specific field to report genetic diseases in future SARE exercises.

However, it is noted that the likelihood of transmitting a multi-factorial genetic disease from the donor to the offspring is sometimes difficult to assess.

As in previous years, the highest proportion of SAE was reported under the “human error” category, especially in the procurement and processing steps. This may suggest the need to further clarify the most critical aspects needing to be addressed when revising standard operating procedures in the tissue establishments and assessing training needs and competencies of the personnel.

The reporting exercise also revealed an increase in the number of reported SAR in donors in the year 2015, in comparison with previous years, indicating that competent authorities support reporting of these SAR so that appropriate follow-up mechanisms for tissue and cell donors are promoted.

⁸ https://ec.europa.eu/health/blood_tissues_organ/policy/evaluation_en

⁹ Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation is a Joint Action co-funded by the European Union.

Overall, the implementation of vigilance requirements and data collection in the field appears to improve over time, as countries are making efforts each year to improve the quality and accuracy of data submitted. However, there is still a significant degree of under-reporting by some countries; thus data should be interpreted with caution. The Commission together with the Member States will reflect on the most appropriate solution for this issue, with the support of the newly established SoHO Vigilance Expert Sub-group.